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EXAMINER	ART UNIT	PAPER NUMBER
SCHEINER L	1813	20

18N1/0906

U.S. PATENT OPERATIONS/[KMP]
M/S 10-2-E-431 AMGEN, INC.
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DATE MAILED: 09/06/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 3/11/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-39 are pending in the application.
   Of the above, claims 1-11, 14, 27-29, 31-34 & 36-39 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 12, 13, 23-26, 30 & 35 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1813.

Since this application is a continuation, not a divisional, filed under 37 CFR 1.62, prosecution is being continued on the invention elected and prosecuted by applicants in the parent application, i.e. Group II, claims 12, 13, 15-26, 30 and 35. See 1046 O.G. 2. Consequently, claims 1-11, 14, 27-29, 31-34 and 36-39 stand withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a nonelected invention.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 12, 13, 23-26, 30 and 35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 13, 23-26, 30 and 35 are vague and indefinite in their recitation of "DNA sequences which hybridize to the DNA

sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) or (b)", "DNA sequence coding for a polypeptide fragment or polypeptide analog of naturally-occurring metalloproteinase inhibitor wherein said polypeptide fragment or polypeptide analog has (a) at its N-terminus at least amino acid residues 1 to 42 of Figure 2; and, (b) one or more of the biological properties of naturally-occurring metalloproteinase inhibitor.", "one or more of the biological properties of naturally occurring metalloproteinase inhibitor", and/or "DNA sequence coding for an analog of human metalloproteinase inhibitor selected from the group consisting of : a) [Met^{-1}] metalloproteinase inhibitor; and b) metalloproteinase inhibitor wherein one or more cysteines are replaced by alanine or serine.". The language is so broad that the metes and bounds of the respective claims cannot adequately be determined. Which fragment is intended? How long is it? The recitation of fragment destroys any limitation intended by the recitation of "at least the amino acid residues 1 to 42 of Figure 2.". Attention is directed to Ex parte Tanksley (26 USPQ2d 1384) wherein the Board noted that, under 35 USC 112, second paragraph, the claims must be so definite as to allow their comparison with the available art and must also make it possible for the public to determine from the claims what it is they comprehend. Only

claims limited to the particular nucleic acid sequence disclosed in Figure 2 of the instant specification are so definite. Again, which cysteines are replaced? Moreover, hybridization conditions have not been set forth where applicable. What stringency is intended? What is intended by the recitation of "analog"? It would appear that chimeric proteins not envisaged would fall within the scope of that which is claimed. What is naturally occurring metalloproteinase inhibitor? Is that human or bovine inhibitor? It would seem that the respective proteins would not have identical biological properties. Again, a member of the public would not know what is intended by that which is claimed.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

The specification is not enabled for the recitation of fragments or analogs since none have been taught and it would require one of ordinary skill in the art an undue amount of experimentation to find those portions of instant protein or analogs having characteristics as claimed. The scope of the

claims is broader than the enablement provided by the specification. That is, fragments are claimed, however, the specification fails in teaching specific fragments having the claimed characteristics. Again the recitation of fragments and analogs of metalloproteinase inhibitor is so broad as to include virtually any portion or type of modification. No guidance is provided as to what portions of the disclosed protein can be modified without changing the activity of the protein nor of what types of modifications are likely to produce an active protein. Therefore, undue experimentation would be required of one of skilled in the art to make fragments and analogs of the MI protein as disclosed. The scope of claims drawn to DNA which hybridizes to instant DNA is also broad since conditions with regard to stringency have not been set forth. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Predictability of which changes can be tolerated in a protein's amino acid sequence while retaining similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the

proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (see the whole publication of Bowie et al. 1990. Science, Vol 247, pp. 1306-1310, particularly p. 1306 and column 2 of p. 1308).

While recombinant and mutagenesis techniques are known and it is known that some proteins can tolerate a number of amino acid substitutions (i.e. predominantly in non-conserved amino acids), the positions within the protein's sequence where such amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and such modifications are unpredictable in the absence of further guidance. Other positions in the sequence of such proteins are **critical** to the protein's structure/function relationship, e.g. such as various positions or regions directly involved in binding, catalysis or other activity and in providing the correct three-dimensional spacial orientation of binding and/or catalytic sites. It is well known that such critical positions can tolerate **only** conservative substitutions or **no** substitutions (see p. 1306, column 2, paragraph 2 of Bowie et al.) and one skilled in the art would expect any tolerance of a

given protein to modification to decrees with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed protein(s), for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation.

While enablement can be supported even if some experimentation is required, such experimentation must be merely routine and if the results to be obtained are unpredictable the experimentation is not routine, but rather **undue**. Applicants have not taught where the critical regions are in the instant protein(s) or related proteins having the same utility nor what amino acid are conserved in the particular claimed protein(s) nor the structural requirements for producing compounds of similar activity/utility. Thus, beyond the mere presentation of sequence data, applicants have provided little or no guidance which would, without **undue** experimentation, enable one of ordinary skill in the art to determine what positions, if any, in the protein are tolerant to change (e.g. such as by amino acid substitutions), the nature and extent of changes that can be made and tolerated in the various positions and what utility will be possessed by

the modified protein(s), particularly in view of the virtually infinite number of compounds encompassed by these claims wherein the polypeptide can include any number of addition, deletions or substitutions. Without such guidance, the changes which can be made in the proteins structure and still maintain activity/ utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). Recently, in Ex parte Maizel (27 USPQ2d 1662), the Board considered that claims encompassing such biologically functional equivalents were analogous to a single means claim and as such were more broad than the disclosure which disclosed only a single specific DNA segment known to the inventor. Such is the case here in which the specification is considered enabling only for claims limited to the specific nucleic acid sequence given in Figure 2.

Claims 12, 13, 23-26, 30 and 35 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 12, 13, 23-26, 30 and 35 are rejected under 35 U.S.C. § 103 as being unpatentable over Murray et al in view of Kimmel for reasons of record.

Any inquiry concerning this communication should be directed to Laurie Scheiner at telephone number (703) 308-1122.

L Sch
Laurie Scheiner/LAS

August 31, 1994

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180